IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TENNESSEE
WESTERN DIVISION

CHARLES R. BAKER,	)	
	)	
Plaintiff,	)	**Case No. 2:10-cv-02273**
	)	
v.	)	**JURY DEMANDED**
	)	
BAUSCH & LOMB, INC., and	)	
ISTA PHARMACEUTICALS, INC.,	)	
	)	
Defendants.	)	

FIRST AMENDED COMPLAINT FOR FALSE PATENT MARKING

Plaintiff CHARLES R. BAKER (hereinafter "Baker" or "Plaintiff"), for his First Amended Complaint against defendants BAUSCH & LOMB, INC (hereinafter "Bausch & Lomb") and ISTA PHARMACEUTICALS, INC. (hereinafter "ISTA"), alleges as follows:

NATURE OF THE CASE

1.

This first amended complaint is filed pursuant to Rule 15 of the Federal Rules of Civil Procedure, which provides that a party may amend the party's pleading once as a matter of course at any time before a responsive pleading is served. The named defendants have not yet answered or otherwise responded to the plaintiff's complaint, and therefore, this first amended complaint is appropriate pursuant to the Federal Rules.

2.

This is a *qui tam* action on behalf of the public for false patent marking under Title 35, Section 292, of the United States Code.

3.

As set forth in detail below, defendant Bausch & Lomb and defendant ISTA have violated 35 U.S.C. § 292(a) by marking certain Xibrom ® products with United States patent number 4,910,225 (the '225 Patent), even though the '225 Patent is expired, and has been expired since January 24, 2009. On information and belief, the defendants – whether acting individually or collectively – mark Xibrom ® branded products with the expired '225 Patent with the intent to deceive competitors and the public, and to gain a competitive advantage in the market.

4.

Plaintiff seeks an award of monetary damages against defendant Bausch & Lomb and against defendant ISTA pursuant to 35 U.S.C. § 292 (b) of up to $500 for each offense, with one-half going to the use of the United States and the other half going to the person bringing the action.

THE PARTIES

5.

Plaintiff is a person residing in Lakeland, Tennessee.

6.

Defendant Bausch & Lomb is a Delaware corporation with its principal place of business in Rochester, New York. Defendant's registered agent for service of process is CT Corporation System, 800 South Gay Street, Suite 2021, Knoxville, TN 37929.

7.

Defendant ISTA is a Delaware corporation with its principal place of business in Irvine, California. Defendant's registered agent for service of process is The Corporation Trust Company, Corporation Trust Center, 1209 Orange Street, Wilmington, DE 19801.

JURISDICTION AND VENUE

8.

This Court has jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

9.

Venue is proper in this District under 28 U.S.C. §§ 1391(c) and 1395(a) because, at least in part, defendant Bausch & Lomb's and defendant ISTA's products that are the subject-matter of this Complaint, were and are advertised, offered for sale, and sold within this District.

10.

This Court has personal jurisdiction over defendant Bausch & Lomb and defendant ISTA because defendants have sold and continue to sell falsely marked products in Tennessee and in this District, and/or in the streams of commerce with

knowledge that said products would be sold in Tennessee and in this District. Upon information and belief, such sales by defendants are substantial, continuous, and systematic.

11.

Plaintiff brings this action under 35 U.S.C. § 292(b), which provides that any person may sue for civil money penalties for false patent marking.

GENERAL ALLEGATIONS

12.

Defendant Bausch & Lomb and defendant ISTA have in the past manufactured and marketed (or caused to be manufactured and marketed), and presently manufacture and market (or cause to be manufactured and marketed), products for sale to the general consuming public, including Xibrom ®.

13.

Defendant Bausch & Lomb and defendant ISTA have manufactured, marketed, and sold, and continue to manufacture, market, and sell, a line of eye care products, including a product commonly known as Xibrom ®.

14.

Xibrom ®, including its packaging and/or labeling, has been and continues to be marked with United States patent number 4,910,225 (hereinafter referred to as the "'225 Patent").

15.

The '225 Patent has expired, but defendant Bausch & Lomb and defendant ISTA nevertheless continue using the improper patent markings on Xibrom ®, with the intent to deceive the public and to gain competitive advantage in the market.

16.

When a patent expires, all monopoly rights to the patent terminate irrevocably. Therefore, a product marked with an expired patent is not currently patented by such expired patent. In other words, the product is unpatented.

17.

Marking products with expired patents is likely to, or at least has the potential to, discourage or deter persons and companies from commercializing competing products, which, in turn, causes harm to the consuming public, including Plaintiff, by quelling product innovation and price competition.

18.

Defendant Bausch & Lomb and defendant ISTA are sophisticated companies with many years of experience applying for and obtaining patents, and therefore know that patents do not have an indefinite duration but, rather, expire.

19.

Upon information and belief, defendant Bausch & Lomb and defendant ISTA employ attorneys in their respective in-house legal departments.

20.

Upon information and belief, attorneys in defendants' respective in-house legal departments are responsible for defendants' intellectual property and marketing, labeling, and advertising law.

21.

Defendants, whether by themselves or by their representatives, cannot genuinely believe that a patent does not expire, and that prospective patent rights continue to apply even after a patent's expiration.

22.

Defendant Bausch & Lomb and defendant ISTA knew that the '225 Patent, marked on Xibrom ® as identified herein, was expired.

23.

After the ‘225 Patent expired, Defendant Bausch & Lomb and defendant ISTA – whether acting individually or collectively – marked, or caused to be marked, Xibrom ® and/or its packaging with the expired patent number.

24.

Defendant Bausch & Lomb and defendant ISTA knew that the patent marked on Xibrom ® as identified herein was expired during time period defendant was marking said product with the expired ‘225 Patent.

25.

Because all monopoly rights in an expired patent have terminated, Defendant Bausch & Lomb and defendant ISTA cannot have any reasonable belief that Xibrom ® is patented or covered by the expired patent marked upon its packaging.

26.

By repeatedly marking Xibrom ® with an expired patent, Defendant Bausch & Lomb and defendant ISTA have committed numerous violations of 35 U.S.C. § 292(a).

27.

Defendant Bausch & Lomb and defendant ISTA have committed such violations of 35 U.S.C. § 292(a) with an intent to deceive competitors and the public.

28.

Plaintiff seeks an award of monetary damages against Defendant Bausch & Lomb and defendant ISTA, one half of which shall be paid to the United States pursuant to 35 U.S.C. § 292(b).

COUNT ONE: THE '225 PATENT

29.

Plaintiff restates and incorporates the foregoing paragraphs as if fully set forth herein.

30.

United States Patent Number 4,910,225 was filed on January 24, 1989, and issued on March 20, 1990. (Please see United States Patent No. 4,910,225, attached hereto as Exhibit 'A').

31.

The '225 Patent expired on January 24, 2009.

32.

Defendant Bausch & Lomb and defendant ISTA have in the past and continue to manufacture, market, and sell to the public the product known as Xibrom ®, marked with the '225 Patent.

33.

Defendant Bausch & Lomb and defendant ISTA – whether acting individually or collectively –have violated 35 U.S.C. § 292(a) by marking, or causing to be marked, the packaging, labeling, and/or product commonly known as Xibrom ® with the ‘225 Patent, and any and all other products marked with the ‘225 Patent, subsequent to the date the patent expired with the intent to deceive the public. (Please see Xibrom ® Label (p.4 of 6), attached hereto as Exhibit ‘B’).

34.

Upon information and belief, Defendant Bausch & Lomb and defendant ISTA knew, on or about the date of expiration, that the ‘225 Patent had expired.

35.

Defendants cannot genuinely believe that the ‘225 Patent applies even after it expired.

36.

Upon information and belief, Defendant Bausch & Lomb and defendant ISTA are sophisticated companies with many years of experience applying for, obtaining, and litigating patents. Defendants have committed substantial resources to patent procurement and enforcement. Upon information and belief, defendants have in-house

legal departments and attorneys working therein who are responsible for defendants' intellectual property and marketing, labeling, and advertising law. As sophisticated companies, with in-house legal counsel that regularly handle patent matters, including but not limited to patent procurement and patent-related litigation, defendants are well-aware of the requirements of 35 U.S.C. § 292.

37.

Defendant Bausch & Lomb and defendant ISTA have falsely marked Xibrom ® as described with the intent to deceive the public, in violation of 35 U.S.C. § 292(a).

38.

Each false marking on the product(s) identified is likely to, or at least has the potential to, discourage or deter persons and companies from commercializing competing products.

39.

Defendants' false marking of products with the '225 Patent after it expired has wrongfully quelled competition with respect to such products, thereby causing harm to Plaintiff, the United States, and the general public.

40.

Defendant Bausch & Lomb and defendant ISTA wrongfully and illegally advertised a patent monopoly which it did not possess and, as a result, has benefitted commercially and financially by maintaining false statements of patent rights.

WHEREFORE, Plaintiff demands a trial by jury and requests that the Court enter judgment as follows:

(a) Enter judgment against Defendants and in favor of Plaintiff for the violations alleged in this Complaint;

(b) Order Defendants to pay a civil monetary fine of up to five hundred dollars ($500) per false marking "offense" (or falsely marked article), or an alternative amount as determined by the Court, one-half of which shall be paid to the United States;

(c) Order Defendants to pay discretionary costs and prejudgment interest;

(d) Award attorney's fees to plaintiff pursuant to 35 USC § 285;

(e) Order an accounting for any falsely marked products not presented at trial and an award by the Court of additional damages for any such falsely marked products; and

(f) Grant Plaintiff such other and further relief, at law or in equity, to which Plaintiff is justly entitled.

DEMAND FOR JURY TRIAL

Pursuant to Fed. R. Civ. P. 38(b), Plaintiff demands a trial by jury on all issues so triable.

Respectfully submitted this 23rd day of April, 2010.

/s/ W. Daniel Miles, III
W. DANIEL "DEE" MILES, III *

/s/ Roman A. Shaul
ROMAN A. SHAUL (TN BPR # 024265)

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EXHIBIT A

PATENT 4,910,225

United States Patent
Ogawa , et al.

4,910,225
March 20, 1990

Locally administrable therapeutic composition for inflammatory disease

Abstract

This invention relates to a locally administrable therapeutic composition for inflammatory disease which is characterized by comprising benzoylphenylacetic acid of the formula ##STR1## (wherein R is a hydrogen or halogen atom), or a salt thereof, or the hydrate of said acid or salt, as active ingredient. An ophthalmic composition according to the invention can treat effectively inflammatory eye disease by topical application, is not an irritant to the eye, and has a superior effect to conventional drugs of the same or similar type. The aqueous composition prepared in accordance with this invention has excellent stability and can be used advantageously as a nasal or otic composition as well as an ophthalmic one in the treatment of inflammatory otic or nasal disease.

Inventors: **Ogawa; Takahiro** (Nishinomiya, **JP**), **Kuribayashi; Yoshikazu** (Kobe, **JP**), **Ushio; Kazumichi** (Nishinomiya, **JP**), **Ohtori; Akira** (Nara, **JP**)

Assignee: **Senju Pharmaceutical Co., Ltd.** (Osaka, **JP**)
A. H. Robins Company, Incorporated (Richmond, VA)

Appl. No.: **07/301,033**

Filed: **January 24, 1989**

Foreign Application Priority Data

Jan 27, 1988 [JP] 63-16683

Current U.S. Class:	**514/561**
Current International Class:	A61K 9/00 (20060101); A61K 31/195 (20060101); A61K 31/185 (20060101); A61K 031/195 ()
Field of Search:	514/561

References Cited [Referenced By]

U.S. Patent Documents

4045576	August 1977	Welstead et al.
4126635	November 1978	Welstead et al.
4568695	February 1986	Moran et al.
4683242	July 1987	Poser

Foreign Patent Documents

0221753	May., 1987	EP
58-201710	Feb., 1984	JP

Other References

Walsh et al., Journal of Medicinal Chemistry, 1989, vol. 27, No. 11, pp. 1379-1388. .
Chem. Abst. 107-(1987)-211870z..

Primary Examiner: Friedman; Stanley J.
Attorney, Agent or Firm: Wenderoth, Lind & Ponack

Claims

What is claimed is:

1. A locally administrable opthalmic, otic or nasal therapeutic composition for the treatment of inflammatory disease of the eye, ear or nasal passage which comprises an anti-inflammatory effective amount of a benzoylphenylacetic acid of the formula ##STR3## wherein R is hydrogen or a halogen atom or a pharmaceutically acceptable salt thereof or a hydrate of said acid or salt in admixture with

(a) an isotonizing agent, and

(b) at least one member of the group consisting of a microbial agent and a preservative.

2. The locally administrable therapeutic composition for inflammatory disease according to claim 1, wherein the water-soluble polymer is polyvinyl pyrrolidone, polyvinyl alcohol, carboxypropylcellulose, hydroxyethylcellulose, hydroxypropylcellulose or sodium salt of polyacrylic acid.

3. The locally administrable therapeutic composition for inflammatory disease according to claim 1, wherein the concentration of the water-soluble polymer is in the range of about 0.1-10 W/W %.

4. The locally administrable therapeutic composition for inflammatory disease according to claim 1, wherein the sulfite is in the form of sodium, potassium, calcium or magnesium salt.

5. The locally administrable therapeutic composition for inflammatory disease according to claim 1, wherein the concentration of the sulfite is in the range of about 0.1-1 W/W %.

6. A composition according to claim 1 in the form of an aqueous solution.

7. A method of treating animals or humans to alleviate inflammation of the eye, nasal passage or ear canal which comprises applying to the eye, nasal passage or ear canal an anti-inflammatory effective amount of a compound of the formula: ##STR4## wherein R is hydrogen or a halogen atom or a pharmaceutically acceptable salt thereof, or a hydrate of said acid or salt, as active ingredient.

8. In a locally administrable stable aqueous therapeutic composition for use in the treatment of inflammatory disease comprising an anti-inflammatory effective amount of a benzoylphenylacetic acid of the formula ##STR5## wherein R is hydrogen or a halogen atom, or a pharmaceutically acceptable salt thereof, or a hydrate of said acid or salt, the improvement wherein said composition contains a stabilizing amount of a water-soluble polymer and a sulfite, the pH of said composition being in the range of about 6-9.

9. A locally administrable opthalmic ointment for the treatment of inflammatory disease of the eye which comprises an anti-inflammatory effective amount of a benzoylphenylacetic acid of the formula ##STR6## wherein R is hydrogen or a halogen atom or a pharmaceutically acceptable salt thereof or a hydrate of said acid or salt in admixture with an eye ointment base.

Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a locally administrable therapeutic composition for inflammatory eye disease as well as nasal or otic inflammatory disease.

More particularly, it relates to a locally administrable therapeutic composition for inflammatory eye as well as for nasal or otic inflammatory disease, which contains as active ingredient a benzoylphenylacetic acid derivative, a salt thereof or the hydrate of said acid or salt.

The other object of the present invention is to provide a stable locally administrable aqueous composition such as eye drop, otic composition and nasal composition containing the above compounds.

2. Description of the Prior Art

That certain benzoylphenylacetic acid derivatives, when orally administered, exhibit anti-inflammatory activity has been reported in detail in Journal of Medicinal Chemistry, Volume 27, pages 1379-1388 (1984), among others. Furthermore, Japanese Laid Open Patent Publication No. 126124/1987 describes pharmaceutical compositions for percutaneous administration which contain these compounds. However, none of the published literature-inclusive of the above-mentioned patent specification-contains any description indicating or suggesting that these medicinal substances are effective against inflammatory disease of the eye, nose or ear when they are administered topically.

For the treatment, with topical application of drugs, of inflammatory ophthalmopathy such as uveitis and conjunctivitis which are most frequently observed in the ophthalmological field, steroid drugs such as dexamethazone have so far been employed. Topical application of steroid drugs to the eye has some apprehension of increasing intraocular pressure to cause glaucoma. And, there is a fear not only of causing corneal perforation when such steroid drugs are applied to patients suffered from corneal herpes, corneal ulcer or the like, but also of induction of corneal herpes, keratomycosis, Pseudomonas infections and the like by the topical application of steroid drugs. As there has been known such-effects as above, steroid anti-inflammatory agents shall be applied with particular care. In spite of such a situation, there has not been known any non-steroid anti-inflammatory agent compatible with steroid anti-inflammatory drugs in effectiveness for the treatment of inflammatory opthalmopathy such as uveitis. Thus, in the present stage in this technical field, for the treatment of inflammatory ophthalmopathy, it is hardly possible not to use steroid anti-inflammatory agents with particular care to avoid the side effects as above-mentioned. Under such circumstances, it is natural that ophthalmological experts are awaiting the appearance of non-steroid drugs which are effectively usable against uveitis or the like.

The present inventors investigated to find out topically applicable drugs with lesser side-effects and with superior effectiveness by which topically applicable drugs having been employed in the treatment of inflammatory ophthalmopathy, i.e. steroid anti-inflammatory agent, can be replaced. As a result, the present inventors unexpectedly found that certain derivatives of benzoylphenylacetic acid are very effective in the treatment of inflammatory ophthalmopathy, especially of uveitis, by topical application, and that the effectiveness of such drugs is compatible with that of conventional steroid anti-inflammatory drugs.

Furthermore, since the inventors obtained the finding that there are some problems that the above-mentioned benzoylphenylacetic acid derivatives are unstable in an aqueous solution with the optimal pH range for a locally administrable therapeutic composition, they extensively investigated in search of the method for the preparation of a stable aqueous solution. As a result, we have succeeded in preparing a stable aqueous composition. Thus, the stable aqueous composition according to the invention are achieved based on the above finding.

While a number of non-steroid compounds fall under the category of anti-inflammatory agents, all of them are not effective in treating inflammatory eye diseases when topically administered to the eye. This is because there are several problems lying before them. First, when topically administered to the eye, a medicinal agent has to pass through the cornea so that it can reach the site of inflammation. Even when it has succeeded in arriving at the site of inflammation, it must remain there in a necessary concentration for a necessary period of time. If it fails to meet these requirements, it will be unable to produce expected therapeutic effects. Furthermore, in case it is irritative to the eye, it is rather possible that the topical administration of the medicinal agent to the eye would cause exacerbation of symptoms. Therefore, great caution and much care are necessary in selecting a medicinal agent for topical administration to the eye. Furthermore, in case of administration in the form of eye drops, it goes without saying that it is desirable that the eye drop is stable for a long period of time in an aqueous solution without decomposition or forming insoluble matters.

Accordingly, it is an object of the invention to solve the above problems and provide a novel and useful agent for ophthalmic use.

Moreover, the other object of the invention is to provide a sufficiently stable aqueous solution such as eye drops, otic solution and nasal solution which contains the above compounds when stored for a long period of time.

SUMMARY OF THE INVENTION

The present invention, which has been completed based on the above finding, provides a therapeutic composition for administration to the eye for the treatment of inflammatory eye diseases which contains as active ingredient a benzoylphenylacetic acid of the formula ##STR2## [wherein R is a hydrogen or halogen atom], or salt thereof, or the hydrate of said acid or salt. In the formula, the halogen atom represented by R is, for example, fluorine, chlorine, bromine or iodine. The above compound to be used in accordance with the invention may be in a salt form. The salt includes alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as calcium salt and magnesium salt, among others, and any salt may suitably be used provided that it can attain the object of the invention. The compounds defined above may be obtained in the form of a hydrate depending on the conditions of synthesis, recrystallization and so forth, and such form may be used in practicing the invention without any inconvenience or trouble.

Further, the above compounds may be unstable when stored in an aqueous solution for a long period of time, and there are some problems in the stability of an aqueous solution containing the compounds. Therefore the inventors extensively investigated the stabilizing method in order to enhance the stability. As a result, unexpectedly, they have succeeded in stabilizing the solution by incorporating a water-soluble polymer and sulfite and adjusting the pH to about 6-9.

DETAILED DESCRIPTION OF THE INVENTION

The compounds to be used as active ingredients in the topically administrable therapeutic compositions for inflammatory eye disease as well as nasal or otic disease in accordance with the invention (although such compositions are occasionally hereinafter referred to as "opthalmic composition according to the present invention", use of this abbreviation does not exclude the application of the composition in the nasal or otic fields) can be produced as described in the above-cited report in Journal of Medicinal Chemistry, Volume 27, pages 1379-1388 (1984) or U.S. Pat. No. 4,045,576, for instance, or by a modification of the method described therein. The ophthalmic compositions according to the invention can be

prepared in the form of eye drops, eye ointments and so on in the same manner as various known compositions for topical administration to the eye. Thus, a compound of the above formula or a mixture of two or more compounds of the above formula is preferably made up into an aqueous or non-aqueous solution or mixed with an ointment base suited for ophthalmic use. On that occasion, an aqueous base generally used in the production of ophthalmic preparations, for example sterile distilled water, is suitably used as the aqueous base and the pH thereof is adjusted to a level suited for topical administration to the eye. It is desirable that an appropriate buffer should be added in adjusting the pH. The pH of the ophthalmic compositions according to the invention is selected with due consideration paid to the stability and topical eye irritativity of the active ingredient, among others. According to the present invention, the stability of an aqueous composition containing the above compounds is remarkably enhanced by incorporating a water-soluble polymer and sulfite, and adjusting the pH to 6.0-9.0, preferably about 7.5-8.5. The eye irritation of the solution is not observed. A water-soluble polymer includes polyvinyl pyrrolidone, carboxypropylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, polyvinyl alcohol, sodium salt of polyacrylic acid an so on. Polyvinyl pyrrolidone is preferred among them. The concentration of a water-soluble polymer is in the range of about 0.1 to 10 w/w%. Sulfite includes sodium, potassium, magnesium, calcium salt and so on. The concentration of sulfite is in the range of about 0.1 to 1.0 w/w %. The pH adjustment is generally conducted with sodium hydroxide or hydrochloric acid, for instance, and it is advisable to form a buffer solution by combined use of, for example, sodium acetate, sodium borate or sodium phosphate and acetic acid, boric acid or phosphoric acid, respectively. The ophthalmic compositions according to the invention may further contain pharmaceutically active ingredients, such as an anti-inflammatory agent of another kind, an analgesic and an antimicrobial, unless they are unfit for the purpose of attaining the object of the invention. Examples of such antiinflammatory agent are indomethacin and pranoprofen. Usable examples of the antimicrobial agents are penicillins, cephalosporins, and synthetic antimicrobial agents of the quinolonecarboxylic acid series. Among these active ingredients for combined use with the active ingredient according to the invention, the anti-inflammatory agent is expected to be synergistic with said active ingredient in the ophthalmic compositions according to the invention. The analgestic is suited for the purpose of alleviating inflammation-associated pain, and the antimicrobial agent is suited for the purpose of preventing secondary infection. It is of course possible to incorporate active agents other than those mentioned above in the ophthalmic compositions according to the invention unless the object of the invention cannot be attained due to the presence thereof.

In preparing the ophthalmic compositions according to the invention as mentioned above, an isotonizing agent, a microbicidal agent or preservative, a chelating agent, a thickening agent and so forth may be added to the compositions in accordance with the general practice of ophthalmic preparation manufacture. The isotonizing agent includes, among others, sorbitol, glycerine, polyethylene glycol, propylene glycol, glucose and sodium chloride. The preservative includes para-oxybenzoic acid esters, benzyl alcohol, parachloro-meta-xylenol, chlorocresol, phenetyl alcohol, sorbic acid and salts thereof, thimerosal, chlorobutanol, and the like. The chelating agent is, for example, sodium edetate, sodium citrate or sodium salt of condensed phosphoric acid. In preparing the ophthalmic compositions according to the invention in the form of eye ointments, the ointment base can be selected from among petrolatum, Macrogol, carboxymethylcellulose sodium, etc.

The ophthalmic composition according to this invention is prepared by incorporating the active compound in a base or vehicle for topical application to the eye. To prepare a liquid preparation, the concentration of the active ingredient may range from about 0.001% to about 10% and is preferably in the range of about 0.01% to about 5%. An ointment may be prepared by using the active compound in a concentration from about 0.001% to about 10%, preferably about 0.01% to about 5%. The ophthalmic composition of this invention may be administered in accordance with the following schedules. In the form of eye-drops, one to several drops per dose are instilled with a frequency of once to 4 times a day according to the clinical condition. Of course, the dosage may be adjusted according to symptoms. The ophthalmic composition according to this invention can be used topically for the treatment of inflammatory diseases of the eye without causing local irritant effects and produces beneficial effects

surpassing those obtainable with the conventional drugs of the same type.

According to this invention, there can be obtained a stable aqueous composition such as otic composition or nasal composition. Other conventional methods can be used unless unsuitable for the object of this invention. Among others, an isotonizing agent, buffer solution and preservatives can be used. The concentrations of the compounds of the invention varies depending on symptoms and so on, and usually may be in the range of about 0.001 to about 10%, preferably about 0.01 to about 5%.

The following experimental examples are given to delineate the efficacy profile of the ophthalmic composition of this invention and the stability of the aqueous compositions of the invention.

EXPERIMENTAL EXAMPLE 1

Anti-inflammatory effect of the ophthalmic agent according to this invention in experimental ophthalmitis induced by bovine serum albumin in white rabbits

[Animals]

Seventeen male white rabbits weighing about 2 kg were used. They were fed with 80 g of Labo RG-RO (Nippon Agricultural Co., Ltd.) daily and had free access to tap water.

[Test drug]

Sodium 3-(4-bromobenzoyl)-2-aminophenylacetate monohydrate (hereafter referred to as Compound [I] was used as 0.5% and 0.1% ophthalmic solutions. These ophthalmic solutions had a pH value of 8.11 and osmolarities of 310 mOsm/kg.multidot.H.sub.2 O and 325 mOsm/kg.multidot.H.sub.2 O, respectively. Bovine serum albumin (hereafter referred to as "BSA") was dissolved in physiological saline to a concentration of 5% and sterilized by filtration. A 0.1 ml portion of the solution was injected into the central part of the vitreus of both eyes using a 27G needle under anesthesia with 0.4% oxybuprocaine hydrochloride to induce ophthalmitis (ophthalmitis I). After 28 days when ophthalmitis I had nearly recovered, 2.5% BSA solution was administered in a dose of 25 mg/ml/kg into the auricular vein to cause ophthalmitis (ophthalmitis II). The severity of ophthalmitis was rated according to the rating scale.sup.(1) of Yamauchi et al., based on the Draize method in which an increased weight given to the internal segment of the eye. Observation was made with a frequency of once in one or two days during the peak period of inflammation and once in three or four days before and after the peak period for ophthalmitis I and 3, 6, 12 and 24 hours after intravenous injection of BSA for ophthalmitis II.

[Results]

Anti-inflammatory effect in ophthalmitis I

Table 1 shows the sum of scores for respective parameters during a peak inflammatory period of 3 days after aseptic injection of 5% BSA into the

central part of the vitreous.

Table 2 shows the amount of protein, white blood cell count and the concentration of prostaglandins in the anterior chamber aqueous humor.

Anti-inflammatory effect in ophthalmitis II

The administration of 2.5 ml/kg of 2.5% BSA solution into the auricular vein after 29 days when the inflammatory symptoms of ophthalmitis I had substantially subsided resulted in a relapse of inflammation after 3 hours in the physiological saline group, where both the external and internal segment of the eye after 12 hours showed inflammatory pictures similar to those observed at the peak of ophthalmitis I. These symptoms were still observed even after 24 hours. Table 3 shows the scores for respective parameters at 3, 6, 12 and 24 hours after the intraveous injection of BSA. Table 4 shows the amount of protein, white blood cell count and the concentration of prostaglandins in the anterior chamber aqueous humor.

Administration of the test drug

Gross observation was made on the day after injection of BSA into the vitreous body and with the animals arranged in the decreasing order of severity of ocular inflammation, grouping was carried out in such a manner that the intensity distribution would be uniform over the groups. Thus, a physiological saline group of 7 animals, a 0.1% Compound [I] instillation group of 4 animals and a 0.5% Compound [I] instillation group of 5 animals were provided. After this grouping procedure, the test drugs and saline were respectively instilled into both eyes of the rabbits, 50 .mu.l per dose, 4 times a day. For induction of ophthalmitis II, each drug was instilled into both eyes, 50 .mu.l per dose, immediately after injection of BSA into the auricular vein and at 1-hour intervals thereafter, for a total of 14 times.

Evaluation of results

In ophthalmitis I, Compound [I] at concentrations of 0.1% and 0.5% caused a potent and dose-dependent inhibition for both the external and the internal segment of the eye. Furthermore, at both concentration levels, Compound [I] produced a substantially complete inhibition of prostaglandins in the aqueous humor in ophthalmitis I.

In regard to the inhibitory effect on inflammatory symptoms, as evaluated by gross observation, which are induced by the intraveous injection of antigen, the Compound [I] according to this invention produced a substantially complete inhibition at both concentrations. As to white blood cell count, all drugs produced nearly the same degree of inhibition in both the internal and the external segments of the eye.

For any of the drugs, no body weight suppression was observed even after 28 consecutive days of treatment. In the organs including the thymus, spleen, adrenal and so on, anatomically no abnormality was found.

EXPERIMENTAL EXAMPLE 2

The effect of the compounds according to this invention on carrageenin edema in rats

Test drugs

1. Sodium 3-(4-bromobenzoyl)-2-aminophenyl-acetate (hereinafter referred to as Compound [I])

2. Sodium 3-(4-chlorobenzoyl)-2-aminophenyl-acetate (hereinafter referred to as Compound [II])

3. Sodium 3-benzoyl-2-aminophenylacetate (hereinafter referred to as Compound [III])

Method

Using female Wister rates weighing 100 g in groups of 5 animals or 10 eyes, 0.05 ml of 1% carrageenin (dissolved in physiological saline at 50.degree. C.) as a phlogogen was injected beneath the conjuctiva of both eyes to induce edema. Physiological saline, as a control, and test drugs were respectively instilled into both eyes 40 and 20 minutes before and immediately after the injection of carrageenin, in the amount of 2.5 .mu.l per dose. Four hours after the phlogogen treatment, each animal was sacrificed by cervical dislocation and in accordance with the method of Maistrello et al..sup.(2), the scalp was peeled off toward the eyelid and the edematous portion together with the skin was removed along the lid margin and weighed. The degrees of inhibition of carrageenin edema in the control group and drug treatment group are shown in Table 5. Each drug group showed a significant difference from the control group, indicating the effectiveness of the three compounds against acute ocular inflammation.

EXPERIMENTAL EXAMPLE 3

Effects on atropine-resistant miosis and on protein increase after paracentesis

The experiment was divided into two parts, i.e. Experiment 3.a, in which the effect of Compound [I] was evaluated, and Experiment 3.b, in which indomethacin, the most known anti-inflammatory drug with strong cyclooxgenase inhibitory activity, was evaluated.

[Test drugs]

The solutions of the following formulas were used.

_____ a. Compound [I] Compound [I] 0.1 0.01 0.001 0.0001% Boric acid 1.0 1.0 1.0 1.0% Borax q.s. q.s. q.s. q.s. Sodium chloride 0.25 0.25 0.25 0.25% Sodium edetate 0.02 0.02 0.02 0.02% Benzalkonium chloride 0.005 0.005 0.005 0.005% Tween 80 0.3 0.3 0.3 0.3% (pH 8.0, Osmotic pressure 310 mOsm/Kg.H.sub.2 O) b. Indomethacin Indomethacin 0.5% Castor oil q.s.

_____

[Animals]

Totally 28 male albino rabbits (4 rabbits.times.7 groups) with a body weight of about 2 kg werr used. They had been confirmed, before the

experiment, to have mydriatic response to 1% atropine for at least 4 hours.

[Test procedure]

50 .mu.l each of 1% atropine solution was instilled into both eyes of the animals one hour before the 1st paracenthesis, in which approx. 0.2 ml/eye of aqueous humor (primary aqueous humor) was collected. Topical application of 50 .mu.l each of the test drug solutions was conducted 30 min before the paracenthesis. Pupil diameter of each eye was measured with a slide caliper immediately before and 10 min after the paracenthesis. The 2nd paracenthesis was conducted 90 min after the 1st one, in which approx. 0.2 ml/eye of aqueous humor (secondary aqueous humor) was collected.

[Results]

As shown in Table 6, Compound [I] exhibited a dose-related inhibitory activity on miosis after paracentesis at the concentrations of 0.0001-0.1%, whereas little effect was observed with indomethacin at the concentrations as high as 0.5%. As shown in Table 7, Compound [I] exhibited a strong and dose-related inhibitory activity on protein increase after paracenthesis, in which the effect of 0.01% of Compound [I] was equivalent to that of 0.5% indomethacin. It is well known that atropine-resistant miosis and protein increase in aqueous humor after paracentesis are caused by prostaglandin E.sub.2, which-is one of the most important chemical mediators of inflammation and is synthesized immediately after mechanical injury. The results, therefore, indicate that Compound [I] has stronger anti-inflammatory effect than indomethacin.

EXPERIMENTAL EXAMPLE 4

_____ Formula _____ Compound [I] 0.1 g Borax 1.0 g Sodium borate Sufficient quantity Sodium chloride 0.25 g Disodium edetate 0.02 g Benzalkonium chloride 0.005 g Polysorbate 80 0.3 g Sterile purified water To make 100 ml _____

Stability was observed at 60.degree. C. of the compound by changing pH (6.0, 7.0, 8.0 and 9.0) of the above formula. The results are shown in Table 8.

Of the above four, the formula at the pH of 8 is most stable. In the formula, the change in residue rate were not almost observed but in three weeks red insoluble matters were observed.

EXPERIMENTAL EXAMPLE 5

As a result of extensive examination on preventing the red insoluble matters, the stability was observed by incorporating polyvinyl pyrrolidone.

_____ Formulas B-1 B-2 _____ Compound [I] 0.1 g 0.1 g Boric acid 1.5 g 1.5 g Borax Sufficient quantity Disodium edetate 0.02 g 0.02 g Benzalkonium chloride 0.007 g 0.007 g Polysorbate 80 0.15 g 0.15 g Polyvinyl pyrrolidone 2.0 g -- Sterile purified water To make 100 ml pH 8 pH 8 _____

In the above formulas, the results of the stability at 60.degree. C. are as follows (Table 9):

It was found that by incorporating polyvinyl pyrrolidone, the appearance of red insoluble matters was considerably prevented. In four weeks, however, some insoluble matters were observed.

EXPERIMENTAL EXAMPLE 6

Moreover, as a result of searching for more stable solutions, the inventors obtained the finding that by further incoporating sodium sulfite other than polyvinyl pyrrolidone, the stability was remarkably increased.

_____ Formulas B B-3 _____ Compound [I] 0.1 g 0.1 g Boric acid 1.5 g 1.5 g Borax Sufficient quantity Disodium edetate 0.02 g 0.02 g Benzalkonium chloride 0.007 g 0.007 g Polyvinyl pyrrolidone 0.15 g 0.15 g Sodium sulfite -- 0.2 g Sterile purified water To make 100 ml pH 8 pH 8 _____

As shown in Table 10, the change of appearance was observed in the formula in which sodium sulfite was not incorporated, and the residue increased by about 7%. By contrast, In the solution containing Compound [I] in which polyvinyl pyrrolidone and sodium sulfite coexist, the change of appearance was not observed at all and the decomposition of Compound [I] was not observed either. It was found that the stability was remarkably enhanced. Thus, there can be successfully obtained a stable aqueous composition containing the compounds.

The following are explanatory examples of the ophthalmic composition and other stable aqueous compositions according to the invention.

EXAMPLE 1

_____ Sodium 3-(4-Bromobenzoyl)-2-aminophenyl- 0.1% acetate monohydrate Boric acid 1.0% Borax Sufficient quantity Sodium chloride 0.25% Sodium edetate 0.02% Benzalkonium chloride 0.005% Polysorbate 80 0.3% Purified water Sufficient quantity _____

The above ingredients are made up into an ophthalmic solution (the total volume being 100 ml) and pH is adjusted to 8.0.

EXAMPLE 2

_____ Sodium 3-benzoyl-2-amino-phenyl- 0.1% acetate Boric acid 1.0% Borax 0.02% Sodium chloride 0.25% Sodium edetate Sufficient quantity Benzalkonium chloride 0.005% Polysorbate 80 0.3% Purified water Sufficient quantity _____

The above ingredients are made up into an ophthalmic solution (the total volume being 100 ml) and pH is adjusted to 8.0.

EXAMPLE 3

Sodium 3-(4-chlorobenzoyl)-2-amino- 1.0% phenylacetate White petrolatum Sufficient quantity

The above ingredients are mixed up into an eye ointment (100 g) in the conventional manner.

EXAMPLE 4

Sodium 3-(4-chlorobenzoyl)-2-amino- 0.01 g phenylacetate monohydrate Carboxymethylcellulose Sufficient quantity

The above ingredients are mixed up in the conventional manner to give 100 g of an eye ointment.

EXAMPLE 5

Sodium 3-(4-chlorobenzoyl)-2-amino- 1.0 g phenylacetate monohydrate Sodium chloride 0.8 g Tween 80 0.2 g Purified water Sufficient quantity

The above ingredients are made up into an ophthalmic solution (the total volume being 100 ml) and the pH is adjusted to 7.5 with hydrochloric acid.

EXAMPLE 6

Ophthalmic Solution

Sodium 3-(4-bromobenzoyl)-2-aminophenyl- 0.1 g acetate monohydrate Boric acid 1.25 g Borax 1.0 g Disodium edetate 0.02 g Benzalkonium chloride 0.005 g Polysorbate 80 0.15 g Polyvinyl pyrrolidone 2.0 g Sodium sulfite 0.2 g Sterile purified water To make 100 ml pH 8

EXAMPLE 7

Ophthalmic Solution

Sodium 3-(4-bromobenzoyl)-2-aminophenyl- 0.1 g acetate monohydrate Boric acid 0.7 g Borax Sufficient quantity Sodium chloride 0.5 g Polysorbate 80 0.15 g Methylparaben 0.013 g Ethylparaben 0.007 g Polyvinyl pyrrolidone 2.0 g Sodium sulfite 0.2 g Sodium edetate 0.02 g Sterile purified water To make 100 ml

EXAMPLE 8

Ophthalmic Solution

Sodium 3-(4-bromobenzoyl)-2-aminophenyl- 0.1 g acetate monohydrate Boric acid 1.5 g Borax Sufficient quantity Benzalkonium chloride 0.005 g Polysorbate 80 0.15 g Polyvinyl pyrrolidone 2.0 g Sodium sulfite 0.1 g Sterile purified water To make 100 ml pH 8

The following (Table 11) are the residue and appearance of the compositions in Examples 6-8 after 4 weeks at 60.degree. C.

As shown in Table 11, it was found that changes in appearances of the compositions were not observed at all, and the decomposition of the compound was not almost observed, the aqueous compositions being stable, excellent for a long period of time.

EXAMPLE 9

Ophthalmic Solution

Sodium 3-(4-bromobenzoyl)-2-aminophenyl- 0.1 g acetate monohydrate Sodium monohydrogen phosphate 0.2 g Sodium dihydrogen phosphate Sufficient quantity Sodium chloride 0.8 g Benzalkonium chloride 0.007 g Polysorbate 80 0.15 g Polyvinyl alcohol 1.0 g Potassium sulfite 0.2 g Sterile purified water To make 100 ml pH 8

EXAMPLE 10

Nasal and Otic Solution

Sodium 3-(4-bromobenzoyl)-2-aminophenyl- 0.1 g acetate monohydrate Boric acid 0.1 g Borax Sufficient quantity Sodium chloride 0.8 g Methylparaben 0.3 g Ethylparaben 0.1 g Polyvinyl pyrrolidone 2.0 g Sodium sulfite 0.1 g Sterile purified water To make 100 ml pH 7.5

TABLE 1 Test Drug Physiological Compound [I] Compound [I] Parameter saline (14).sup.a 0.1% (8).sup.a 0.5% (10).sup.a

External Segment Corneal opacity 2.5 .+-. 0.5 1.0 .+-. 0.4 (60.0).sup.b 0.4 .+-. 0.2 *.sup.2 (48.0).sup.b Palpebral cunjunctival 3.8 .+-. 0.5 1.3 .+-. 0.2 *.sup.2 (65.8).sup.b 1.5 .+-. 0.3 *.sup.2 (36.8).sup.b injection Palpebral conjunctival 0.7 .+-. 0.3 0.1 .+-. 0.1 (85.7).sup.b 0 *.sup.2 (100).sup.b edema Balbar conjunctival 6.5 .+-. 0.7 4.5 .+-. 0.6 (30.8).sup.b 1.6 .+-. 0.2 *.sup.1 (74.5).sup.b injection Discharge 0.3 .+-. 0.1 0 *.sup.1 (100).sup.b 0 *.sup.3 (100).sup.b Total Score 13.7 .+-. 1.9 6.8 .+-. 1.0 *.sup.1 (50.4).sup.b 3.5 .+-. 0.4 *.sup.3 (74.5).sup.b Internal Segment Anterior chamber 3.0 .+-. 0.3 3.6 .+-. 0.8 (-20.0).sup.b 2.0 .+-. 0.4 (33.3).sup.b opacity Iridic injection 6.1 .+-. 0.6 2.6 .+-. 0.2 *.sup.3 (57.4).sup.b 1.8 .+-. 0.2 *.sup.3 (70.5).sup.b Morphological 4.4 .+-. 0.2 2.9 .+-. 0.4 *.sup.2 (34.1).sup.b 2.9 .+-. 0.4 *.sup.2 (34.1).sup.b change of iris Total Score 13.5 .+-. 0.8 9.1 .+-. 1.0 *.sup.2 (32.6).sup.b 6.6 .+-. 0.8

*.sup.3 (51.1).sup.b External + Internal Grand Total Score 27.3 .+-. 2.5 15.9 .+-. 1.8 *.sup.2 (41.8).sup.b 10.1 .+-. 1.0 *.sup.3 (63.0).sup.b

[Notes to Table 1 Each value represents the mean .+-. standard error. The figure in parentheses.sup. a represents the number of cases, and the figure in parentheses.sup. b represents the degree (%) of inhibition relative to th physiological saline group. Significant differences from the physiologica saline group at the levels of *.sup.1 = $p < 0.05$, *.sup.2 = $p < 0.01$ and *.sup.3 = $p < 0.001$.

TABLE 2 Concentration Number Protein White Blood Cell Prostaglandin Drug % of Cases mg/Mml Cells/mm.sup.3 ng/ml

Physiological -- 7 50.3 .+-. 7.3 5869 .+-. 2194 1.89 .+-. 0.75 saline Compound [I] 0.1 4 48.7 .+-. 3.8 5593 .+-. 3436 <0.4.sup.a 0.5 5 28.4 .+-. 1.6*.sup.1 1980 .+-. 654 <0.4.sup.a

[Notes to Table 2 Each value represents the mean .+-. standard error; .sup.a means that the concentration is less than the assay limit (0.4 ng/ml); *.sup.1 means a significant difference from the physiological saline group at $p < 0.05$.

TABLE 3 Test Drug Physiological Compound [I] Compound [I] Parameter saline (14).sup.a 0.1% (8).sup.a 0.5% (10).sup.a

1/10 External Segment Corneal opacity 1.4 .+-. 0.3 0.6 .+-. 0.2 (57.1).sup.b 0.6 .+-. 0.2 (57.1).sup.b Palpebral conjunctival 5.7 .+-. 0.7 4.0 .+-. 0.3 (29.8).sup.b 3.7 .+-. 0.1 *.sup.1 (60.5).sup.b injection Palpebral conjunctival 2.0 .+-. 0.8 1.1 .+-. 0.4 (45.0).sup.b 0.9 .+-. 0.2 (55.0).sup.b edema Balbar conjunctival 11.1 .+-. 0.6 8.1 .+-. 0.4 (27.0).sup.b 8.1 .+-. 0.3 *.sup.2 27.0).sup.b injection Discharge 0.3 .+-. 0.1 0 (100).sup.b 0 (100).sup.b Total Score 20.5 .+-. 2.5 13.1 .+-. 1.1 *.sup.1 (32.7).sup.b 13.3 .+-. 0.6 *.sup.1 (31.4).sup.b Internal Segment Anterior chamber 1.9 .+-. 0.3 2.8 .+-. 0.8 (-47.4).sup.b 2.8 .+-. 0.5 (-47.4).sup.b opacity Iridic injection 7.3 .+-. 0.8 2.8 .+-. 0.1 *.sup.2 (61.6).sup.b 3.3 .+-. 0.3 *.sup.2 (54.8).sup.b Morphological 4.3 .+-. 0.5 2.4 .+-. 0.4 *.sup.2 (44.2).sup.b 2.9 .+-. 0.3 *.sup.1 (32.6).sup.b change of iris Total Score 13.5 .+-. 1.1 8.0 .+-. 1.2 *.sup.2 (40.7).sup.b 9.0 .+-. 0.7 *.sup.2 (33.3).sup.b External + Internal Grand Total Score 33.9 .+-. 3.5 21.8 .+-. 2.1 *.sup.1 (35.7).sup.b 22.3 .+-. 1.1 *.sup.1 (34.2).sup.b

[Notes to Table 3 Each value represenets the mean .+-. standard error. The figure in parentheses .sup.a represents the number of cases, and the figure in parentheses .sup.b represents the degree (%) of inhibition relative to th physiological saline group. Significant differences from the physiologica saline group at the levels of *.sup.1 = $p < 0.05$, and *.sup.2 = $p < 0.01$.

TABLE 4 Concentration Number Protein White Blood Cell Prostaglandin Drug % of Cases mg/Mml Cells/mm.sup.3 ng/ml

Physiological -- 10 39.5 .+-. 2.20 2416 .+-. 478 15.79 .+-. 4.86 saline Compound [I] 0.1 8 48.7 .+-. 3.8 1489 .+-. 499 <0.4.sup.a *.sup.1 0.5 10 28.4 .+-. 1.6*.sup.1 1673 .+-. 277 <0.4.sup.a *.sup.2

[Notes to Table 4 Each value represents the mean .+-. standard error; .sup.a means that the concentration is less than the assay limit (0.4 ng/ml); *.sup.1 means a significant difference from the physiological saline group at the level o *.sup.1 = $p < 0.05$, and *.sup.2 = $p < 0.01$.

TABLE 5 Weight of Degree of Concentration Edema* inhibition Compound (%) (mg) (%)

Compound [I] 1.0 43.93 .+-. 4.138 16.9** 2.5 36.323 .+-. 3.308 31.3** Compound [III] 1.0 30.98 .+-. 3.194 41.4** 5.0 32.80 .+-. 2.409 37.9** Control -- 52.17 .+-. 2.401 -- Compound [II] 0.5 37.52 .+-. 2.423 36.9** 1.0 39.02 .+-. 3.057 34.4** Control -- 59.47 .+-. 3.057 -- [Notes to Table 5 *Each value represents the mean .+-. standard error for 10 eyes. **Significant differences from the control group at p<0.001.

TABLE 6 Test drug Content (%) Miosis (%) Inhibition (%) Physiological -- 23.7 .+-. 1.94 -- saline Exp. 3, a 0.1 17.4 .+-. 3.80 24.9 .+-. 16.4 0.01 15.4 .+-. 1.60 *2 35.2 .+-. 6.75 0.001 19.0 .+-. 1.44 19.7 .+-. 6.08 0.0001 21.5 .+-. 1.97 9.2 .+-. 8.33 Physiological -- 17.6 .+-. 1.88 -- saline Indomethicin 0.5 16.4 .+-. 3.86 6.0 .+-. 21.4 t-test *2: P < 0.01

Table 7 Primary aqueous Secondary aqueous Test humor humor Inhibition drug Content (%) Protein (.mu.g/ml) Protein (.mu.g/ml) (%) Physiological saline 0.89 .+-. 0.20 25.04 .+-. 4.12 --M -Exp. 3, b 0.1 0.76 .+-. 0.20 3.06 .+-. 0.46 *2 87.8 0.01 0.39 .+-. 0.04 *1 9.29 .+-. 7.30 *2 62.9 0.001 0.38 .+-. 0.02 *1 18.45 .+-. 3.53 26.3 0.0001 0.44 .+-. 0.06 23.45 .+-. 1.67 6.3 Physiological saline 0.84 .+-. 0.11 20.21 .+-. 1.79 -- Indomethacin 0.5 0.77 .+-. 0.10 6.13 .+-. 1.64 *3 69.7 test *1: P < 0.05 *2: P < 0.01 *3: P < 0.001

TABLE 8 Formula pH Appearance Residue (%) 1 Week A-1 pH 6.0 + 38.6 2 pH 7.0 + 79.3 3 pH 8.0 - 100.5 4 pH 9.0 - 101.1 2 Weeks A-1 pH 6.0 + 23.9 2 pH 7.0 + 63.7 3 pH 8.0 - 98.6 4 pH 9.0 - 99.4 3 Weeks A-1 ph 6.0 + 19.3 2 pH 7.0 + 54.2 3 pH 8.0 - 98.0 4 pH 9.0 - 99.0 Note: The symbol "-" denotes that change in appearance was not observed. The symbol "+" denotes that change in appearance was observed. (hereinafter, the same as above)

TABLE 9 Formula 1 Week 2 Weeks 4 Weeks B-1 - - - B-2 - - +

TABLE 10 Formula Residue (%) Appearance B-1 93.4 + B-3 100.9 -

TABLE 11 Appearance Residue (%) Example 6 - 100.9 Example 7 - 99.2 Example 8 - 98.9

* * * * *

Images

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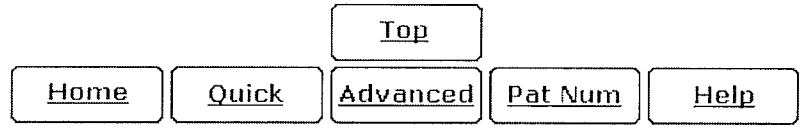


EXHIBIT B

XIBROM ® LABEL

Your Search Terms: PATENT LOMB

Version 3 - Published Mar 01, 2010

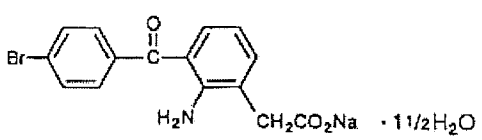
XIBROM - bromfenac sodium solution
Ista Pharmaceuticals, Inc

XIBROM™ (bromfenac ophthalmic solution) 0.09%

Sterile

DESCRIPTION

XIBROM (bromfenac ophthalmic solution) 0.09% is a sterile, topical, nonsteroidal anti-inflammatory drug (NSAID) for ophthalmic use. Each mL of Xibrom contains 1.035 mg bromfenac sodium (equivalent to 0.9 mg bromfenac free acid). Bromfenac sodium is designated chemically as sodium 2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate, with an empirical formula of $C_{15}H_{11}BrNNaO_3 \cdot 1\frac{1}{2}H_2O$. The structural formula of bromfenac sodium is:



Bromfenac sodium is a yellow to orange crystalline powder. The molecular weight of bromfenac sodium is 383.17. XIBROM ophthalmic solution is supplied as a sterile aqueous 0.09% solution, with a pH of 8.3. The osmolality of XIBROM ophthalmic solution is approximately 300 mOsmol/kg. Each mL of XIBROM ophthalmic solution contains: **Active:** bromfenac sodium hydrate 0.1035%. **Inactives:** benzalkonium chloride (0.05 mg/mL), boric acid, disodium edetate (0.2 mg/mL), polysorbate 80 (1.5 mg/mL), povidone (20 mg/mL), sodium borate, sodium sulfite anhydrous (2 mg/mL), sodium hydroxide to adjust the pH, and water for injection, USP.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Bromfenac is a nonsteroidal anti-inflammatory drug (NSAID) that has anti-inflammatory activity. The mechanism of its action is thought to be due to its ability to block prostaglandin synthesis by inhibiting cyclooxygenase 1 and 2.

Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure.

Pharmacokinetics:

The plasma concentration of bromfenac following ocular administration of 0.09% XIBROM (bromfenac ophthalmic solution) in humans is unknown. Based on the maximum proposed dose of

one drop to each eye (0.09mg) and PK information from other routes of administration, the systemic concentration of bromfenac is estimated to be below the limit of quantification (50 ng/mL) at steady-state in humans.

Clinical Trials:

Clinical efficacy was evaluated in two randomized, double-masked, vehicle-controlled U.S. trials in which subjects with a summed ocular inflammation score ≥3 after cataract surgery were assigned to XIBROM or vehicle in a 2:1 ratio following surgery. One drop of XIBROM or vehicle was self-instilled in the study eye twice a day for 14 days, beginning the day after surgery. The primary endpoint was reduction of ocular inflammation (to trace inflammation or clearing) assessed 14 days post-surgery using a slit lamp binocular microscope. In the intent-to-treat analyses of both studies, a significant effect of XIBROM on ocular inflammation after cataract surgery was demonstrated (62-66% vs. 40-48%). An additional efficacy endpoint was the time required for resolution of ocular pain in subjects who reported pain. Overall, only 20% of patients undergoing cataract surgery in these trials had pain on the first day after surgery. In these patients, the XIBROM group demonstrated a statistically significant difference in median time to resolution of ocular pain of 2 days compared to 4 days for patients receiving vehicle.

INDICATIONS AND USAGE

XIBROM ophthalmic solution is indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.

CONTRAINDICATIONS

XIBROM ophthalmic solution is contraindicated in patients with known hypersensitivity to any ingredient in the formulation.

WARNINGS

Contains sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With some NSAIDs, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

PRECAUTIONS

General:

All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases

(e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post surgery may increase patient risk for the occurrence and severity of corneal adverse events.

It is recommended that XIBROM ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Information for Patients:

XIBROM ophthalmic solution should not be administered while wearing contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac

up to 0.6 mg/kg/day (360 times the recommended human ophthalmic dose [RHOD] of 1.67 µg/kg in 60 kg person on a mg/kg/basis, assuming 100% absorbed) and 5.0 mg/kg/day (3000 times RHOD), respectively revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (540 and 180 times RHOD, respectively).

Pregnancy:

Teratogenic Effects: Pregnancy Category C.

Reproduction studies performed in rats at oral doses up to 0.9 mg/kg/day (540 times RHOD) and in rabbits at oral doses up to 7.5 mg/kg/day (4500 times RHOD) revealed no evidence of teratogenicity due to bromfenac. However, 0.9mg/kg/day in rats caused embryo-fetal lethality, increased neonatal mortality, and reduced postnatal growth. Pregnant rabbits treated with 7.5 mg/kg/day caused increased post-implantation loss.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-Teratogenic Effects:

Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of XIBROM ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers:

Caution should be exercised when XIBROM ophthalmic solution is administered to a nursing woman.

Pediatric Use:

Safety and efficacy in pediatric patients below the age of 18 have not been established.

Geriatric Use:

There is no evidence that the efficacy or safety profiles for XIBROM differ in patients 65 years of age and older compared to younger adult patients.

ADVERSE REACTIONS

The most commonly reported adverse experiences reported following use of XIBROM after cataract surgery include: abnormal sensation in eye, conjunctival hyperemia, eye irritation (including burning/stinging), eye pain, eye pruritus, eye redness, headache, and iritis. These events were reported in 2-7% of patients.

Clinical Practice:

The following events have been identified during postmarketing use of bromfenac ophthalmic solution 0.09% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical bromfenac ophthalmic solution 0.09%, or a combination of these factors, include corneal erosion, corneal perforation, corneal thinning, and epithelial breakdown (see **PRECAUTIONS, General:**).

DOSAGE AND ADMINISTRATION

For the treatment of postoperative inflammation in patients who have undergone cataract extraction, one drop of XIBROM ophthalmic solution should be applied to the affected eye(s) two times daily beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the postoperative period.

HOW SUPPLIED

XIBROM™ (bromfenac ophthalmic solution) 0.09% is supplied in a white LDPE plastic squeeze bottle with a 15 mm LDPE white dropper-tip and 15 mm polypropylene gray cap as follows:

NDC 67425-004-50

5 mL in 10 cc container

NDC 67425-004-12

2.5 mL in 7.5 cc container

Storage

Store at 15-25°C (59-77°F)

Rx Only

U.S. Patent No. 4,910,225

Manufactured for: ISTA Pharmaceuticals, Inc.
Irvine, CA 92618

by: Bausch & Lomb Incorporated
Tampa, FL 33637

Under license from: Senju Pharmaceutical Co., Ltd.
Osaka, Japan 541-0046

Revised November 2008
Printed in USA

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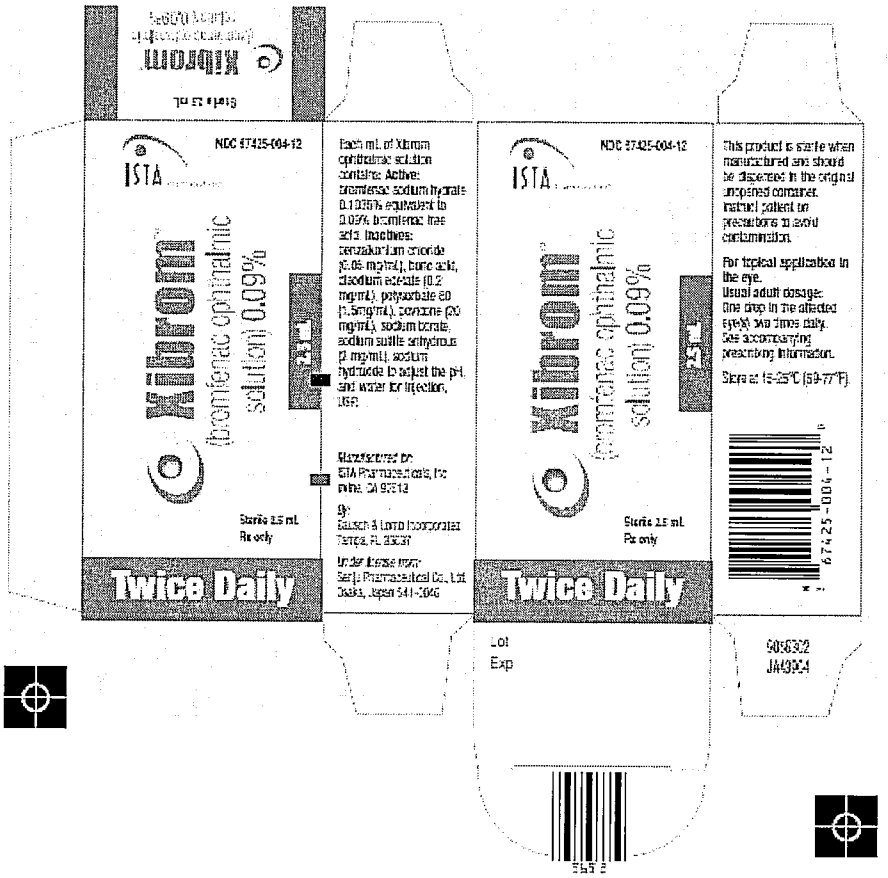

NDC 67425-004-12

Xibrom™ (bromfenac ophthalmic solution) 0.09%

Sterile 2.5 mL
Rx only
Twice Daily

Each mL of Xibrom ophthalmic solution contains:

Active: bromfenac sodium hydrate 0.1035% equivalent to 0.09% bromfenac free acid.

Inactives: benzalkonium chloride (0.05 mg/mL), boric acid, disodium edetate (0.2 mg/mL), polysorbate 80 (1.5mg/mL), povidone (20mg/mL), sodium borate, sodium sulfite anhydrous (2mg/mL), sodium hydroxide to adjust the pH, and water for injection, USP.

This product is sterile when manufactured and should be dispensed in the original unopened container. Instruct patient on precautions to avoid contamination.

For topical application in the eye.
Usual adult dosage:
One drop in the affected eye(s) two times daily. See accompanying prescribing information.

Store at 15-25°C (59-77°F).

XIBROM bromfenac sodium solution			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**NDC Product Code (Source)**	67425-004

Route of Administration	OPHTHALMIC	DEA Schedule

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
BROMFENAC SODIUM (BROMFENAC)	BROMFENAC SODIUM	1.035 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
BENZALKONIUM CHLORIDE	0.05 mg in 1 mL
BORIC ACID	11 mg in 1 mL
EDETATE DISODIUM	0.2 mg in 1 mL
POLYSORBATE 80	1.5 mg in 1 mL
POVIDONE	20 mg in 1 mL
SODIUM BORATE	11 mg in 1 mL
SODIUM HYDROXIDE	
SODIUM SULFITE	2 mg in 1 mL
WATER	

Product Characteristics

Color	Score
Shape	Size
Flavor	Imprint Code
Contains	

Packaging

#	NDC	Package Description	Multilevel Packaging
1	67425-004-50	1 BOTTLE In 1 CARTON	contains a BOTTLE, DROPPER
1		5 mL In 1 BOTTLE, DROPPER	This package is contained within the CARTON (67425-004-50)
2	67425-004-12	1 BOTTLE In 1 CARTON	contains a BOTTLE, DROPPER
2		2.5 mL In 1 BOTTLE, DROPPER	This package is contained within the CARTON (67425-004-12)

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021664	01/05/2005	

Labeler - Ista Pharmaceuticals, Inc (957212350)

Establishment

Name	Address	ID/FEI	Operations
Ista Pharmaceuticals, Inc		957212350	ANALYSIS

Establishment

Name	Address	ID/FEI	Operations
Bausch & Lomb Incorporated		222207751	ANALYSIS, MANUFACTURE

Revised: 06/2009 Ista Pharmaceuticals, Inc